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| APPLICATION NO.                                                                          | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|------------------------------------------------------------------------------------------|-------------|----------------------|---------------------|------------------|
| 10/678,891                                                                               | 10/03/2003  | Rosanne Bonjouklian  | X-13338A            | 2326             |
| 25885                                                                                    | 7590        | 04/08/2004           | EXAMINER            |                  |
| ELI LILLY AND COMPANY<br>PATENT DIVISION<br>P.O. BOX 6288<br>INDIANAPOLIS, IN 46206-6288 |             |                      | HUANG, EVELYN MEI   |                  |
|                                                                                          |             | ART UNIT             | PAPER NUMBER        | 1625             |

DATE MAILED: 04/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

|                              |                        |                     |  |
|------------------------------|------------------------|---------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b> | <b>Applicant(s)</b> |  |
|                              | 10/678,891             | BONJOUKLIAN ET AL.  |  |
|                              | <b>Examiner</b>        | <b>Art Unit</b>     |  |
|                              | Evelyn Huang           | 1625                |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE \_\_\_\_\_ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on \_\_\_\_\_.
- 2a) This action is **FINAL**.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 18-28,30,31 and 45-55 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 18-28,30,31 and 45-55 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
    - a) All    b) Some \* c) None of:
      1. Certified copies of the priority documents have been received.
      2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
      3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |                                                                                                                                    |                                                                             |
|------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                               | Paper No(s)/Mail Date. _____.                                               |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____. | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
|                                                                                                                                    | 6) <input type="checkbox"/> Other: _____.                                   |

## **DETAILED ACTION**

1. Claims 18-28, 30-31, 45-55 are pending. Claims 1-17, 29, 32-44 have been canceled according to the preliminary amendment filed on 10-3-2003.

### ***Priority***

2. The instant is a divisional of 10/088721. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

### ***Duplicate Claims***

3. Claims 30, 31 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 45, 47 respectively. The pharmaceutical carrier recited in claims 30, 31 does not further limit the pharmaceutical composition of claims 45, 47 respectively. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

### ***Claim Rejections - 35 USC § 112(1)***

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Art Unit: 1625

Claims 18-28, 30, 31, 45-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The following evaluation factors have been considered.

a. *Nature of the invention.*

The instant invention is drawn to a composition comprising the inventive compound and one or more oncolytic agents, and the method of inhibiting a resistant neoplasm, or a neoplasm susceptible to resistance with the inventive compound in combination with one or more oncolytic agents.

b. *State of the prior art and the level of the skill in the art.*

There are at least two proteins known to be involved in multiple drug resistance (MDR): P-glycoprotein (P-gp) and MRP-related proteins (MRP1), which are discovered more recently. These two proteins have different substrate specificity and tissue distribution (Armistead, 5717092, columns 1-2, PTO-1449; Marbeuf-Gueye et al. Molecular Pharmacology, 1998, 53:141-147, pages 141-2; Lawrence et al. J. Med. Chem. 2001, 44: 594-601, pages 594; Germann et al. Anti-Cancer Drugs, 1997, 8 :141-155, pages 141-142). The over-expression of MRP1 is not consistently found in tumor cells (Lawrence, page 594, column 2). At the time of the invention, as recited by the Applicant (page 2 of the specification), it is unknown what determines whether a cell line will acquire resistance via a MDR1 or MRP1 mechanism, a selective MRP1 inhibitor has not been described, as MRP1 inhibitor art is still at its infancy stage. A synthetic compound, biricodar (VX-710), having a structure very different from the instant, has been shown to inhibit both MRP1 and P-gp (Germann, page 141). The enhancement of activity in combination of an oncolytic agent *in vivo* has not been shown.

At the time of the invention, a correlation between the inhibition of P-gp and/or MRP1 and the reversal of the drug resistance has not been established. While some of the MDR inhibitors have been shown to reverse the resistance *in vitro*, results in patients have been disappointing (Peck et al. Journal of Clinical Oncology, 2001, 19(12):3130-41, page 3130-1).

Pharmacokinetic interaction between the chemotherapeutic drugs and the MDR modulators is also known to occur (Peck, page 3131, column 1).

The level of the skill in the MDR art is high.

c. *Predictability/unpredictability of the art.*

The high degree of unpredictability is well recognized in the pharmaceutical art. A slight modification in the structure of the compounds would drastically alter the antagonist activity and selectivity for MRP1 or Pgp as demonstrated for the structurally similar quinoxalinone compounds (Lawrence, page 596, Tables 2-3).

d. *Amount of guidance/working examples.*

***How to make***

Since pharmacokinetic interaction between the chemotherapeutic drugs and the MDR modulators is known to occur (Peck, page 3131, column 1) the specific combination with particular oncolytic agent(s) and the amount of the active ingredients in the multiple active ingredient composition would be of critical importance. However, an example of a pharmaceutical composition comprising the inventive compound and one or more oncolytic agents has not been described.

***How to use***

The references for the inhibition assays of P-gp and MRP1 are found on page 137 of the specification. The results for specific compounds are not shown. Assay for reversal of MRP1-mediated doxorubicin resistance and MDRI-mediated vincristine resistance in HL60 cell line is described on page 138 of the specification. The results are generally described as ‘representative compounds of formula I demonstrated a significant effect in reversing the MRP1 multiple drug resistance. Many of the compounds showed very significant enhancement of activity in combination with the oncolytic agent as opposed to the oncolytic agent alone. In addition, a large majority of the compounds tested displayed a significant degree of selective inhibition of the HL60/adr cell line over the HL60/Vinc cell line’ (page 138, line 30 to page 139, line 3).

In vivo procedures are not found in the specification.

e. *The breadth of the claims.*

Applicant’s assertion that the inventive compound in combination with any oncolytic agent(s) would be effective in inhibiting *any* resistant neoplasm or *any* neoplasm susceptible to resistance, does not commensurate with the scope of the objective enablement, especially in view

of the high degree of unpredictability in the art, and the absence of working examples directed to specific compounds (paragraphs b, c, d above).

f. *Quantitation of undue experimentation.*

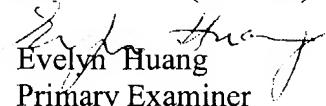
As the MRP1 inhibitor art is still in its infancy stage, and a correlation between the inhibition of MRP1 and the reversal of the drug resistance has not been established, in view of the high degree of unpredictability in the art, the absence of specific working examples and the fact that the breadth of the claims does not commensurate with that of the objective enablement, the disclosure as presented would not allow one of ordinary skill in the art to make and/or use all the invention as claimed without undue experimentation (paragraphs b-e above).

***Conclusion***

5. No claims are allowed.
6. Gruber (6369070) discloses a MRP1 inhibiting isoxazoloquinolone compound similar to the instant. However, the proviso in the instant claims has set a demarcation from Gruber's compound.
7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 571-272-0686. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
Evelyn Huang  
Primary Examiner  
Art Unit 1625